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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Johnson et al.

Serial No.: 09/764,734

Filed: January 17, 2001

For: ANTIMICROBIAL COMPOSITIONS

Edgewater, New Jersey 07020
June 21, 2001

SUBMISSION OF PRIORITY DOCUMENT

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Sir:

Pursuant to rule 55(b) of the Rules of Practice in Patent Cases, Applicant(s) is/are submitting herewith a certified copy of the United Kingdom Application No. 0001133.8 filed January 18, 2000, and United Kingdom Application No. 0001132.0 filed January 18, 2000, upon which the claim for priority under 35 U.S.C. § 119 was made in the United States.

It is respectfully requested that the priority document be made part of the file history.

Respectfully submitted,

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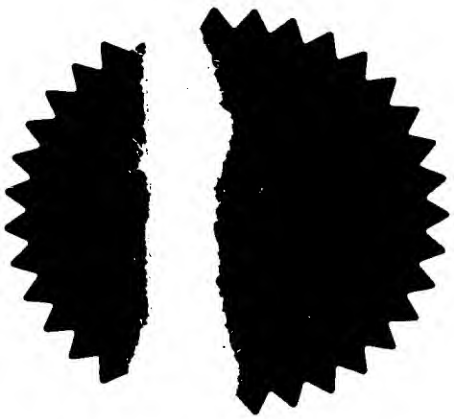

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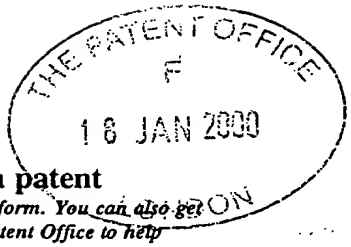

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2.	Patent application number *(The Patent Office will fill in this par*	**0001132.0** 18 JAN 2000
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	Patents ADP number *(if you know it)*	1628002
	If the applicant is a corporate body, give the country/state of its incorporation	**UNITED KINGDOM**
4.	Title of the invention	**ANTI-MICROBIAL PRODUCTS**
5.	Name of your agent *(if you have one)*	**ELLIOTT, Peter William**
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ANTI-MICROBIAL PRODUCTS

Field of Invention

This invention relates to the field of anti-microbial compositions and to methods of reducing microbial numbers. In particular, this invention is concerned with reducing microbial numbers upon the surface of the human body and thereby reducing body odour. The compositions and methods involved utilise transition metal chelators having organic counter-ions, together with an additional high efficacy organic anti-microbial agent. When used on the human body, the compositions and methods of the invention are of greatest benefit when used on the most malodorous areas of the body, for example the underarm areas or feet.

Background

Anti-microbial compositions may function by a variety of means. When used upon the human body, such compositions may significantly reduce microbial numbers either by reducing perspiration or by directly affecting the micro-organisms on the body surface as represented by skin. It is with this latter class of compositions, often called deodorant compositions, that this invention is largely concerned.

Most deodorant compositions reduce the number of viable micro-organisms on the surface of the skin. It is well known that sweat is usually odourless until it has been degraded by the skin microflora. Typical deodorants include ethanol and triclosan (2',4,4'-trichloro,2-hydroxy-diphenyl ether) which is a well known anti-microbial agent. However, the deodorising effect obtained with such deodorants wears

off with the passage of time and the microflora progressively recover their numbers.

There is, therefore, a continuing requirement for effective and long lasting deodorant compositions on the market. Hence, the problem to be solved is not simply reducing microbial numbers on the body surface; equally important is maintaining low microbial numbers (particularly low bacterial numbers) on the body surface (particularly in the most malodorous areas, eg. the axillae).

Certain transition metal chelators have previously been incorporated into deodorant compositions. US 4,356,190 (Personal Products Co.) discloses the use of selected aminopolycarboxylic acid compounds for inhibiting the formation of short chain fatty acids by Corynebacterium on the skin surface. For topical application, alkanolamine salts are stated to be preferred. Especially preferred salts are stated to be di- and trialkanolamine salts such as triethanolamine, diethanolamine, and triisopropylamine salts. No mention is made of the use of an additional high efficacy anti-microbial agent.

It should be noted that the selection of counter-ions for chelators in deodorant compositions has a bearing on a further problem common in the field of deodorant compositions: that of compatibility of components and stability of products (see later).

WO 97/02010 (Procter and Gamble Co.) discloses the use of chelators selected from the succinic acid, glutaric acid, and phosphonic acid classes as bactericidal compounds. Mixtures with conventional bactericidal agents are also disclosed. Chelators with organic counter-ions are not

disclosed and the only chelator salt actually exemplified is trisodium ethylenediamine disuccinate (Na_3EDDS).

WO 97/44006 (Ciba Speciality Chemicals Holding, Inc.) claims the use of nitrogen-containing complexing agents for the anti-microbial treatment of the skin and of textile fibre materials. Particular complexing agents mentioned include those formed from neutralising EDDS with ethanolamine or laurylamine. The use of 20% ethanol in a deodorant stick comprising a chelator is also disclosed; however, no mention is made of additional high efficacy anti-microbial agents.

WO 97/01360 (Concat Ltd.) claims a method of inhibiting bacterial growth using particular substituted polyaza compounds that show affinity for first series elements. It is stated that compatible salts may be formed by neutralisation with inorganic or organic bases, including primary, secondary and tertiary amines, notably ethanolamine, diethanolamine, morpholine, glucamine, N,N-dimethylglucamine, and N-methylglucamine. Compositions are stated to optionally contain pharmaceutically acceptable auxiliaries; however, no mention is made of additional anti-microbial agents, although the use of anhydrous ethanol is exemplified in an example including a chelator trisodium salt.

Other patents indicate that transition metal chelators can improve the efficacy of particular known anti-microbials. WO 98/12399 (Public Health Research Institute of the City of New York) discloses improved performance of lanthionine-containing bacteriocins in compositions also comprising a transition metal chelator. WO 97/09974 (Laboratoire Medix) discloses compositions comprising chlorhexidine and a chelator. EP 0019670 B1 (Glyco Chemicals, Inc.) discloses anti-microbial compositions comprising a condensation

product of 5,5-dimethyl hydantoin and formaldehyde in combination with a water-soluble chelating agent selected from ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA) or the alkali metal salts thereof. US 4,199,602 (Economics Laboratory, Inc.) discloses the potentiation of anti-microbial nitroalkanes by aminocarboxylic-type chelating agents. US 5,688,516 (University of Texas System et al) discloses compositions comprising non-glycopeptide anti-microbials (other than vancomycin) in combination with a selection of components, including a chelating agent. WO 99/10017 (University of Texas System et al) discloses a method for controlling the growth of micro-organisms using a chelating agent and an anti-microbial agent. GB 1,420,946 (Beecham Group Ltd.) discloses that the activity of selected phenolic anti-microbials can be vastly increased by certain chelating agents, in particular the disodium salt of EDTA. None of this group of patents refers to the use of chelators having organic counter-ions.

Chelators have also been disclosed as formulation aids in deodorant products. US 5,798,094 (Gillette Company) discloses the use of 0.3 to 1.6% of an alkali metal salt of a chelating agent in cosmetic sticks to help achieve clarity; US 5,516,511 (Procter and Gamble Co.) discloses particular antiperspirant gel compositions in which chelators are used during manufacture to prevent reaction between the active and the primary gellant; and US 5,849,276 (Procter and Gamble Co.) mentions chelants in antiperspirant stick compositions, although such materials are stated to be optional "non-active" components.

Summary of the Invention

This invention is concerned with the amelioration of the two problems of anti-microbial compositions alluded to above: the problem of obtaining prolonged anti-microbial activity, together with the problem of obtaining compatibility of components and the stability of products.

It has now been discovered that prolonged anti-microbial activity may be obtained by using a transition metal chelator having an organic counter-ion in combination with a further high efficacy organic anti-microbial agent. In addition, said components have good compatibility and can be formulated together in stable compositions. The prolonged anti-microbial activity often manifests itself as a long-lasting deodorancy benefit and the good stability is attributable to compatibility between the components of the compositions.

An additional benefit of the compositions of the invention is that they can, if desired, be formed with relatively low levels of water. This can be of value in compositions applied to the human body, as compositions containing relatively high levels of water can sometimes cause an undesirable wet sensation on application. It can also be of benefit with regard to container choice: low water content compositions enable metal containers to be used with less risk of corrosion. A further benefit of compositions having low water levels is their compatibility with additional hydrophobic components, for example perfume components (see "Perfumery: practice and principles", R.R.Calkin and S.Jellinek, [Wiley, 1994, p171]).

Thus, according to a first aspect of the present invention, there is provided an anti-microbial product comprising a

transition metal chelator having an organic counter-ion and a further organic anti-microbial agent having a minimum inhibitory concentration (MIC) of 1 $mg.ml^{-1}$ or less. (The abbreviation 'FOAM' is frequently used for 'further organic anti-microbial agent' in this specification.)
In certain preferred embodiments, such anti-microbial products function as deodorant products.

According to a second aspect of the present invention, there is provided a method of controlling microbial numbers, said method comprising the application to a substrate of a transition metal chelator having an organic counter-ion and a FOAM having a minimum inhibitory concentration (MIC) of 1 $mg.ml^{-1}$ or less. Particular embodiments of this aspect of the invention involve the control of microbial numbers on the surface of the human body for example skin which is representative of an external surface populated by microorganisms which generate odour from body secretions and the resulting control of malodour of the human body, using said method.

According to a third aspect of the present invention, there is provided a method for the manufacture of an anti-microbial composition comprising the formation of a mixture of an organic anti-microbial agent having a minimum inhibitory concentration (MIC) of 1 $mg.ml^{-1}$ or less and the product of the at least partial neutralisation of an acidic transition metal chelator with an organic base.

Detailed Description

The novel products of the invention perform unexpectedly well in terms of anti-microbial efficacy and maintenance of

low malodour, particularly when applied to the human body. Without wishing to be bound by theory, it is hypothesised that after reduction of microbial numbers by the FOAM and/or by other components within the composition and/or by some external treatment like washing, the chelator salt effectively inhibits the up-take of essential transition metal ion nutrients by the remaining microbes, thereby minimising their re-growth. In addition, the invention offers significant advantages in terms of compatibility of components and product stability. Forming chelator salts with organic counter-ions enables good compatibility with a wide range of FOAMs, enabling both components to function effectively and for them to be co-formulated in stable compositions, when desired.

It is not essential that the chelator salt and the FOAM are part of the same composition. The anti-microbial benefit derived from use of the invention may be gained by independent application of the chelator salt and the FOAM. Such application may be concurrent or consecutive, provided that the treated substrate experiences the presence of both components at the same time. When the components are applied from independent compositions, it is preferred that the product also comprises a means for, and/or instruction for, both of the compositions to be applied to the substrate requiring treatment.

It is preferred that the anti-microbial product of the invention comprises a transition metal chelator and a FOAM that are both present in the same composition. The benefits found with such compositions can include good product aesthetics, lack of product separation, attainment of the desired rheology, visco-stability, good dispensing, and any combination of these benefits or others.

The method of controlling microbial numbers offered by the invention is particularly useful because the benefit can extend for many hours, for example 5 hours, or 24 hours, or even longer, after application of the product to the substrate. When the substrate is the skin of the human body, this can result in an extended deodorancy benefit; that is to say, extended inhibition of generation of human body odour.

The chelator salt and FOAM may be present in composition or compositions of the invention in any form. For example, either or both of the agents may be used neat or may be diluted with a volatile propellant and used as an aerosol; with an additional liquid and used, for example, as a roll-on or squeeze-spray product; or with a thickener or structurant and used, for example, as a cream, gel or solid stick product.

The anti-microbial product of the invention may be applied to the substrate requiring treatment by any means. Frequently, the substrate requiring treatment is a surface. Application of liquid compositions can be by absorption onto a carrier matrix like paper, fabric, or sponge and application by contacting said carrier matrix with the surface. Solid or semi-solid compositions can be applied by direct contact or can be dissolved or dispersed in a liquid medium prior to application. Application can also comprise a combination of any two or more of the above techniques.

When the FOAM is amphoteric or cationic, it is particularly important to use chelator salts with organic counter-ions, in accord with the present invention. This is particularly true of cationic FOAMs, and especially true of polycationic FOAMs. In this context, "polycationic" means possessing more than one positive charge, although the importance of the use

of chelator salts with organic counter-ions is even greater in the presence of polycationic FOAMs that possess more than five positive charges per molecule.

Chelators

Preferred transition metal chelator salts possess anions having affinity for iron (III), preferably high affinity for iron (III); that is to say, a binding constant for iron (III) of greater than 10^{10}, or, for optimum performance, greater than 10^{26}. The 'iron (III) binding constant' referred to above is the absolute stability constant for the chelator-iron (III) complex. Such values are independent of pH and consider only the most anionic, fully deprotonated form of the chelator. Measurements can be made potentiometrically, and in a number of other ways. Full details of suitable methods can be found in "Determination and Use of Stability Constants", A.E.Martell and R.J.Motekaitis (VCH, New York, 1989). Tables of applicable values may be found in numerous sources, for example "Critical Stability Constants", R.M.Smith and A.E.Martell (Plenum Pub. Corp., 1977).

Preferred chelator salts are formed from chelators which are able to significantly inhibit the growth of a relevant micro-organism when present, in a medium containing said micro-organism, at a concentration of 3×10^{-6} $mol.dm^{-3}$ or less. Inhibition is considered significant when growth of the relevant micro-organism on a supporting medium can be reduced by at least 30%, preferably by at least 45%. When the surface to be treated is human skin, a relevant micro-organism is *Staphlococcus epidermidis* and chelators capable of achieving significant inhibition include

diethylenetriaminepentaacetic acid (DTPA) and triethylenetetraaminehexaacetic acid (TTHA), but exclude ethylenediaminetetraacetic acid (EDTA) and trans-1,2-diaminocyclohexane-N,N,N',N'-tetraacetic acid (CDTA).

The chelators used in the present invention preferably have acid forms with at least two ionisable acid groups. The acid groups are preferably carboxylic and/or phosphonic, but may be sulphonic or phosphinic, or any mixture of these groups.

Preferred chelators with phosphonic acid groups are, in the acid form, diethylenetriaminepenta(methylphosphonic) acid (DTPMP), ethanehydroxydiphosphonic acid (EHDP), ethylenediaminetetra(methylenephosphonic acid) (EDTMP), and hexamethylenediaminetetra(methylenephosphonic acid) (HMDTMP).

Particularly suitable chelators for use include polycarboxylate compounds, in particular aminopolycarboxylate compounds. The acid forms of the aminopolycarboxylate compounds include EDTA, CDTA, and ethylenediaminedisuccinic acid (EDDS). More preferred aminopolycarboxylate chelators have the acid forms DTPA, TTHA, and ethylenebis[2-(2-hydroxyphenyl)glycine] (EDDHA).

The chelator salts preferably have only moderate molecular weight, by which it is meant that the chelators, in their acid forms, have a molecular weight of less than 1000, more preferably 200 to 800, and most preferably 290 to 580, and in their salt form have a molecular weight of less than 2000, more preferably 300 to 1400, and most preferably 500 to 1000.

The chelator salt is preferably incorporated into a composition at a level of 0.01% to 10%, more preferably at a level of 0.05% to 5%, and most preferably at a level 0.3% to 3% by weight of the non-volatile components of the composition. Mixtures of chelator salts may also be used.

Herein, non-volatile components are those having a boiling point greater than 20°C at atmospheric pressure.

Organic Counter-ions

Any organic counter-ion can be used. The aim is to form a chelator salt that is compatible with the FOAM also present, in addition to any components present in the same composition as the chelator. The salts may be the result of complete or partial neutralisation of the chelator acid groups by an organic base. Also included are salts where the chelator acid groups are partially neutralised with an organic base and partially neutralised with an inorganic base.

Preferred chelator salts are those with nitrogen-containing counter-ions, in particular chelator salts with counter-ions which are protonated or quaternised amines. Salts formed using aliphatic amines are generally preferred to those formed from aromatic amines. Especially preferred cations of the chelator salts are protonated or quaternised amines with at least one N-substituent comprising a C_1-C_{10} terminal hydrocarbyl group. Such relatively hydrophobic organic counter-ions lead to particularly good compatibility between the chelator salt and the organic anti-microbial.

Herein, hydrocarbyl groups are radicals comprising solely carbon and hydrogen atoms.

Preferred protonated or quaternised amine cations of the chelator salts are of formula $R^1R^2R^3R^4N^{(+)}$, wherein R^1 is H or CH_3; R^2, R^3, and R^4 are each independently H or an aliphatic or aromatic substituent containing 0 to 3 hydroxyl groups, optionally interrupted and/or substituted by functional groups such as ether, amine, ester, or amide; with the provisos that at least one of R^2, R^3, or R^4 comprises a C_1-C_{10} terminal hydrocarbyl group, optionally R^2 and R^3 together forming a ring as the terminal hydrocarbyl group, and that R^2, R^3, and R^4 are not all $CH_2CH(OH)CH_3$ groups.

Of the aforementioned preferred transition metal chelators of formula $R^1R^2R^3R^4N^{(+)}$, particularly preferred are transition metal chelators having cations characterised in that at least one of R^2, R^3, or R^4 comprises an H atom directly attached to an N atom or an O atom. The presence of an H atom directly attached to an O atom (ie. a hydroxyl group) in at least one of R^2, R^3, or R^4 is especially preferred, up to the aforementioned limit of 3 hydroxyl groups per N-substituent.

Other particularly preferred transition metal chelator salts have cations comprising N-substituents (R^1, R^2, R^3, and R^4, according to the formula) that collectively contain a total of 0 to 3 hydroxyl groups, preferably 0 to 2 hydroxyl groups.

In many desirable chelator salts, each N-substituent (R^1, R^2, R^3, and R^4, according to the formula) contains not more than one hydroxyl group.

Especially preferred chelator salts are salts of aliphatic amines, characterised in that, in said amines, the ratio of the total number of H atoms directly attached to an N atom or an O atom to the total number of carbon atoms is not greater than 3:4.

Partial salts of chelator acids possessing more than one acidic group may also be employed; such salts retain one or more non-ionised acid groups. Also claimed are salts where the cations are in part protonated or quaternised amines and in part some other cation, for example an alkali metal cation, in particular a sodium ion. Whilst such mixed ionisation states are acceptable, it is preferred that the chelator salts of the invention have at least 40% of their available acid groups in the form of salts with protonated or quaternised amines, in particular protonated or quaternised amines possessing a C_1-C_{10} terminal hydrocarbyl group.

When amines are used to form the chelator salts of the invention, the following preferences apply:

It is preferred that the chelator salt is of an amine of relatively low odour. This is of potential benefit during manufacture and during selection and use of compositions comprising such amine salts. Related to this point is the preference for the amine to have relatively low volatility: a boiling point of 130°C or greater at atmospheric pressure being preferred.

It is preferred that the chelator salt is of an amine that is a liquid, at room temperature and atmospheric pressure. This can be of advantage with regard to formulation and processing.

Preferred chelator salts are salts of isopropanolamine, 2-amino-2-ethyl-1,3-propanediol, 2-(N,N-dimethylamino)-2-methyl-1-propanol and N,N-dimethylaminoethanol. Particularly preferred chelator salts are salts of 2-amino-2-methyl-1-propanol (AMP), diisopropanolamine, 2-aminobutan-1-ol, and cyclohexylamine.

Further Organic Anti-microbial Agents (FOAMs)

The FOAM is a different agent from the transition metal chelator having an organic counter-ion. The FOAM must have a minimum inhibitory concentration (MIC) of 1 $mg.ml^{-1}$ or less, preferably 200 $\mu g.ml^{-1}$ or less, particularly 100 $\mu g.ml^{-1}$ or less. The MIC of an anti-microbial agent is the minimum concentration of the agent required to significantly inhibit microbial growth. Inhibition is considered "significant" if an 80% or greater reduction in the growth of an inoculum of a relevant micro-organism is observed, relative to a control medium without an anti-microbial agent, over a period of 16 to 24 hours at 37°C. The "relevant micro-organism" used for testing should be representative of those associated with the substrate to be treated. When the substrate to be treated is human skin, a relevant micro-organism is Staphylococcus epidermidis. Other relevant micro-organisms include Coryneform spp., Salmonella spp., Escherichia Coli, and Pseudomonas spp., in particular P. aeruginosa. Details of suitable methods for determining MICs can be found in "Antimicrobial Agents and

Susceptibility Testing", C.Thornsberry, (in "Manual of Clinical Microbiology", 5th Edition, Ed. A. Balows et al, American Society for Microbiology, Washington D.C., 1991). A particularly suitable method is the Macrobroth Dilution Method as described in Chapter 110 of above publication (pp. 1101-1111) by D. F. Sahm and J. A. Washington II. MICs of organic anti-microbials suitable for inclusion in the compositions of the invention are triclosan: 0.01-10 $\mu g.ml^{-1}$ (J.Regos et al., Dermatologica (1979), 158: 72-79) and farnesol: ca. 25 $\mu g.ml^{-1}$ (K. Sawano, T. Sato, and R. Hattori, Proceedings of the 17th IFSCC International Conference, Yokahama (1992) p.210-232). By contrast ethanol and similar alkanols have MICs of greater than 1 $mg.ml^{-1}$.

The organic nature of the further anti-microbial agent aids compatibility with the organic salt of the chelator and also with any other organic components present in the composition, for example an alcohol. For some applications it is preferred that the anti-microbial agent is soluble in a C_2-C_3 alcohol, in particular ethanol. Levels of incorporation are preferably from 0.01% to 3%, more preferably from 0.03% to 0.5% by weight of the non-volatile components of the composition. The ratio of FOAM to chelator salt is preferably 1:25 to 1:1.

Preferred FOAMs are bactericides, for example quaternary ammonium compounds, like cetyltrimethylammonium salts; chlorhexidine and salts thereof; and diglycerol monocaprate, diglycerol monolaurate, glycerol monolaurate, and similar materials, as described in "Deodorant Ingredients", S.A.Makin and M.R.Lowry, in "Antiperspirants and Deodorants", Ed. K. Laden (1999, Marcel Dekker, New York). More preferred anti-

microbials for use in the compositions of the invention are polyhexamethylene biguanide salts (also known as polyaminopropyl biguanide salts), an example being Cosmocil CQ™ available from Zeneca PLC, preferably used at up to 1% and more preferably at 0.03% to 0.3% by weight; 2',4,4'-trichloro,2-hydroxy-diphenyl ether (triclosan), preferably used at up to 1% by weight of the composition and more preferably at 0.05-0.3%; and 3,7,11-trimethyldodeca-2,6,10-trienol (farnesol), preferably used at up to 1% by weight of the composition and more preferably at up to 0.5%.

It should be noted that compositions comprising cationic or amphoteric FOAMs, in particular cationic FOAMs, make it particularly important to use the chelator salts that accord with the present invention.

Optional Additional Components

A carrier material for the chelator salt and/or the FOAM agent is a highly desired additional component of the products of the invention. The carrier material may be hydrophobic or hydrophilic, solid or liquid. Preferred carrier materials are liquids. Hydrophobic liquids suitable for use with the chelator salts of the invention include liquid silicones, that is to say, liquid polyorganosiloxanes. Such materials may be cyclic or linear, examples include Dow Corning silicone fluids 344, 345, 244, 245, 246, 556, and the 200 series; Union Carbide Corporation Silicones 7207 and 7158; and General Electric silicone SF1202. Alternatively, non-silicone hydrophobic liquids may be used. Such materials include mineral oils, hydrogenated polyisobutene, polydecene, paraffins, isoparaffins of at least 10 carbon atoms, and aliphatic or aromatic ester oils (eg. isopropyl myristate, lauryl

myristate, isopropyl palmitate, diisopropyl sebecate, diisopropyl adipate, or C_8 to C_{18} alkyl benzoates).

Hydrophilic liquid carrier materials, for example water, may also be employed.

Particularly preferred liquid carrier materials comprise organic solvents. To aid compatibility between the chelator salt and the organic solvent, especially preferred organic solvents are relatively hydrophilic, having a c.logP of less than 2, especially −2 to 1, and in particular −0.5 to 0.5. c.logP is the calculated logarithm to the base 10 of the octanol:water partition coefficient; a method for calculating such values may be found in "Computer-assisted computation of partition coefficients from molecular structures using fragment constants", J.Chou and P.Jurs, J. Chem. Inf. Comput. Sci., 19, 172 (1979). In addition, preferred organic solvents have a melting point of less than 10°C, preferably less than 5°C; this can benefit both low temperature storage stability and ease of manufacture. A class of preferred organic solvents are aliphatic alcohols (monohydric or polyhydric, preferably having 2 to 8 carbon atoms) and polyglycol ethers, preferably oligoglycol ethers having only 2 to 5 repeat units. Examples include dipropylene glycol, glycerol (c.logP −1.538) propylene glycol (c.logP −1.06), butylene glycol (c.logP −0.728), ethanol (c.logP 0.235), propanol (c.logP 0.294), isopropanol (c.logP −0.074), and industrial methylated spirits. The most preferred organic solvents are aliphatic alcohols, in particular those having 2 to 3 carbon atoms, especially ethanol and isopropanol.

Mixtures of carrier materials may also be used. The amount of carrier material employed is preferably from 30% to 99%,

more preferably 60% to 98%, expressed as a weight percentage of the total weight of non-volatile components of the composition.

When organic solvent is present in the composition, it is preferably present at from 30% to 98% by weight of the total weight of the liquid components of the composition; more preferably the organic solvent comprises from 60% to 97% by weight of the total liquids present.

For some applications, it is desired that less than 50% by weight of water is present as part of the liquid components of the composition, more preferably less than 10%. For some preferred compositions, the ratio of other liquid components to water is between 95:5 and 99:1, by weight. In such compositions the chelator salts of the invention have particular solubility and compatibility advantages.

Preferred compositions with an organic solvent comprise a solution of the chelator salt in said organic solvent. Such solutions are preferably homogeneous, preferably having an absorbance, relative to the solvent, of less than 0.2, especially less than 0.1 (for a 1 cm pathlength at 600 nm) measured using a Pharmacia Biotech Ultrospec 200 Spectrophotometer or similar instrument.

Inorganic anti-microbial agents may also be used in the compositions of the invention. Such materials often also can function as anti-perspirant actives when present at a suitable concentration. Examples are often selected from astringent active salts, including, in particular, aluminium, zirconium and mixed aluminium/zirconium salts, including both inorganic salts, salts with organic anions and complexes.. Preferred astringent salts include

aluminium, zirconium and aluminium/zirconium halides and halohydrate salts, such as chlorohydrates. When included, preferred levels of incorporation are from 0.5% to 60%, particularly from 5% to 30% or 40% and especially from 5% or 10% to 30% or 35% by weight of the composition. Especially preferred aluminium halohydrate salts, known as activated aluminium chlorohydrates, are described in EP 6,739 (Unilever PLC and NV). Zirconium aluminium chlorohydrate actives are also preferred materials, as are the so-called ZAG (zirconium-aluminium-glycine) complexes, for example those disclosed in US 3,792,068 (Procter and Gamble Co.). Zinc phenol sulphonate may also be used, preferably at up to 3% by weight of the composition.

Structurants and emulsifiers are further additional components of the compositions of the invention that are highly desirable in certain product forms. Structurants, when employed, are preferably present at from 1% to 30% by weight of the composition, whilst emulsifiers are preferably present at from 0.1% to 10% by weight of the composition. In roll-ons, such materials help control the rate at which product is dispensed by the roll ball. In stick compositions, such materials can form gels or solids from solutions or suspensions of the chelator salt in a carrier fluid. Suitable structurants for use in such compositions of the invention include cellulosic thickeners such as hydroxy propyl cellulose and hydroxy ethyl cellulose, and dibenzylidene sorbitol. Emulsion pump sprays, roll-ons, creams, and gel compositions according to the invention can be formed using a range of oils, waxes, and emulsifiers. Suitable emulsifiers include steareth-2, steareth-20, steareth-21, ceteareth-20, glyceryl stearate, cetyl alcohol, cetearyl alcohol, PEG-20 stearate, and dimethicone copolyol. Suspension aerosols, roll-ons, sticks, and creams require structurants to slow sedimentation (in fluid compositions)

and to give the desired product consistency to non-fluid compositions. Suitable structurants include sodium stearate, stearyl alcohol, cetyl alcohol, hydrogenated castor oil, synthetic waxes, paraffin waxes, hydroxystearic acid, dibutyl lauroyl glutamide, alkyl silicone waxes, quaternium-18 bentonite, quaternium-18 hectorite, silica, and propylene carbonate. Some of the above materials also function as suspending agents in certain compositions.

Further emulsifiers desirable in certain compositions of the invention are perfume solubilisers and wash-off agents. Examples of the former include PEG-hydrogenated castor oil, available from BASF in the Cremaphor RH and CO ranges, preferably present at up to 1.5% by weight, more preferably 0.3 to 0.7% by weight. Examples of the latter include poly(oxyethylene) ethers.

Certain sensory modifiers are further desirable components in the compositions of the invention. Such materials are preferably used at a level of up to 20% by weight of the composition. Emollients, humectants, volatile oils, non-volatile oils, and particulate solids which impart lubricity are all suitable classes of sensory modifiers. Examples of such materials include cyclomethicone, dimethicone, dimethiconol, isopropyl myristate, isopropyl palmitate, talc, finely-divided silica (eg. Aerosil 200), polyethylene (eg. Acumist B18), polysaccharides, corn starch, C12-C15 alcohol benzoate, PPG-3 myristyl ether, octyl dodecanol, C7-C14 isoparaffins, di-isopropyl adipate, isosorbide laurate, PPG-14 butyl ether, glycerol, hydrogenated polyisobutene, polydecene, titanium dioxide, phenyl trimethicone, dioctyl adipate, and hexamethyl disiloxane.

Fragrance is also a desirable additional component in the compositions of the invention. Suitable materials include

conventional perfumes, such as perfume oils and also include so-called deo-perfumes, as described in EP 545,556 and other publications. These latter materials may also qualify as FOAMs. Levels of incorporation are preferably up to 4% by weight, particularly from 0.1% to 2% by weight, and especially from 0.7% to 1.7% by weight.

It should be noted that certain components of compositions perform more than one function. Such components are particularly preferred additional ingredients, their use often saving both money and formulation space. Examples of such components include ethanol, isopropyl myristate, and the many components that can act as both structurants and sensory modifiers, for example silica.

Further additional components that may also be included are colourants and preservatives, for example C_1-C_3 alkyl parabens.

Product Forms

The chelator salts and FOAMs of the invention may be used from any form. Examples include wax-based sticks, soap-based sticks, compressed powder sticks, roll-on suspensions or solutions, emulsions, gels, creams, squeeze sprays, pump sprays, and aerosols. Each product form contains its own selection of additional components, some essential and some optional. The types of components typical for each of the above product forms may be incorporated in the corresponding compositions of the invention. Roll-on compositions particularly suited to the invention are simple solutions in organic solvents, although water can be tolerated in such compositions. In addition, emulsion compositions, for example oil-in-water and water-in-oil emulsions, are not excluded. Stick compositions of the invention are

preferably based on either a monohydric or polyhydric alcohol organic solvent base. They are often gelled with sodium stearate, although dibenzylidene sorbitol (DBS) may alternatively be used, preferably in combination with hydroxypropyl cellulose.

Aerosol Compositions

In one especially desirable aspect of the present invention, the chelator salt, organic anti-microbial, and other optional components are diluted with propellant to form aerosol compositions. This places a particular challenge upon the compositions of the invention, as it requires stability and compatibility of components to be maintained at elevated pressure in the presence of an often highly hydrophobic propellant. Preferred anti-microbial aerosol products comprise an organic solution of a chelator salt and an additional anti-microbial according to the invention, in combination with a non-chlorinated volatile propellant. Particularly preferred variants of such compositions comprise an organic solvent having a c.logP of less than 2 and are homogeneous solutions.

The aerosol composition often comprises from 30 to 99 parts by weight, and particularly 50 to 95 parts by weight of propellant and the remainder (respectively 70 to 1 and particularly 50 to 5 parts by weight) of the deodorant base composition.

The propellant is normally selected from liquefied hydrocarbons or halogenated hydrocarbon gases (particularly fluorinated hydrocarbons such as 1,1-difluoroethane and/or 1-trifluoro-2-fluoroethane) that have a boiling point of below 10°C and especially those with a boiling point below 0°C. It is especially preferred to employ liquefied

hydrocarbon gases, and especially C_3 to C_6 hydrocarbons, including propane, isopropane, butane, isobutane, pentane and isopentane and mixtures of two or more thereof. Preferred propellants are isobutane, isobutane/isopropane, isobutane/propane and mixtures of isopropane, isobutane and butane.

Other propellants that can be contemplated include alkyl ethers, such as dimethyl ether or compressed non-reactive gasses such air, nitrogen or carbon dioxide.

The base composition, which is mixed with the propellant, may comprise any of the following components as preferred additional ingredients: an organic solvent of c.logP less than 2 (eg. ethanol), a fragrance, or an emollient/co-solvent (eg. isopropyl myristate or propylene glycol).

The aerosol formulation can incorporate, if desired, anticlogging agents in conventional amounts, in order to prevent or minimise the occurrence of solid occlusions in the spray nozzle.

The aerosol composition is usually filled into an aerosol canister that is capable of withstanding pressures generated by the formulation, employing conventional filling apparatus and conditions. The canister can conveniently be a metal canister commercially available fitted with a dip tube, valve and spray nozzle through which the formulation is dispensed.

Methods of Manufacture

The details of the relevant methods of manufacture depend upon the product form concerned. However, for single composition products according to the invention, the methods of manufacture available may be categorised into one of two routes: one may form the transition metal chelator salt and then mix the chelator salt with a FOAM; or, alternatively, one may perform an in situ formation of the transition metal chelator in the presence of the FOAM. The in situ route is most applicable for transition metal chelator salts formed by neutralisation or part-neutralisation of an acidic transition metal chelator with an organic base.

Examples

(Note that "letter" codes refer to Comparative Examples.)

The following example illustrates the improved deodorancy performance of compositions comprising a cationic anti-microbial and a chelator with an organic counter-ion.

The performance of the compositions was assessed using deodorancy tests performed according to the following protocol:

The panel employed comprised 50 individuals who had been instructed to use control ethanolic deodorant products during the week prior to the test. At the start of the test, panellists were washed with unfragranced soap and test product (0.3 g) applied to one axilla and control product applied to the other. (Product application was randomised to take into account any left/right bias). Panellists were instructed not to consume spicy food or alcohol, and not to wash under their own axillae, during the duration of the test. A minimum of three expert assessors determined the

intensity of axillary odour at 5 hours and 24 hours after application, scoring the intensity on a scale of 1-5. After each 24 hour assessment, the panellists were re-washed, and products re-applied, as above. The procedure was repeated 4 times. At the end of the test the data were analysed using standard statistical techniques.

Comparative Example B (see Table 1A) was prepared in the following manner. 1.0 g of DTPA (as the free acid) was added to 30 g of water. The pH was adjusted to about 7.0 by dropwise addition of 1M sodium hydroxide solution. 0.5 g of a 20%(w/v) aqueous solution of poly(hexamethylenebiguanide) chloride (PHMBC) was then added to this solution. 0.65 g of hydroxypropylcellulose (HPC) was added to 60 g of ethanol whilst shearing at a speed of about 8000 rpm on a Silverson L4RT mixer (ex. Silverson, Chesham, Bucks.). A homogenous solution was obtained, which was allowed to cool to ambient temperature. 1.5 g of fragrance oil was then added with stirring. The ethanolic HPC solution was then mixed with the aqueous solution of DTPA and the total weight adjusted to 100g with water.

Comparative Example A (see Table 1A) was prepared in a similar manner, with the omission of the DTPA and sodium hydroxide solution.

Table 1A: PHMBC vs. PHMBC/DTPA (sodium salt)

Component		Example A	Example B
PHMBC[1]		0.1	0.1
Na_3DTPA[2]		0	1.15
Ethanol		60	60
HPC[3]		0.65	0.65
Fragrance		1.5	1.5
Water		to 100	to 100
Mean malodour intensity[4]	5 hour	1.38	1.44
	24 hour	1.86	2.05

All components are expressed as weight per cent of the total composition.

1. Poly(hexamethylenebiguanide) chloride, Cosmocil CQ ex Zeneca PLC.
2. DTPA trisodium salt, prepared as in previous examples.
3. Hydroxypropylcellulose, Klucel, ex Hercules.
4. The malodour difference between the compositions was significant at the 95% level after 24 hours.

The results in Table 1A indicate that addition of DTPA trisodium salt to an anti-microbial composition also comprising PHMBC leads to a poorer deodorancy performance.

Example 1 (see Table 1B) was prepared in the following manner. 1.0 g of DTPA (as the free acid) was added to 30 g of water. The pH was adjusted to about 7.0 by dropwise addition of AMP. 0.65 g of HPC and 0.043 g of poly(hexamethylenebiguanide) stearate (PHMBS, as described in WO98/56252 [Unilever PLC and NV]) were added to 60 g of

ethanol whilst shearing at a speed of about 8000 rpm on a Silverson L4RT mixer (ex. Silverson, Chesham, Bucks.) A homogenous solution was obtained, which was allowed to cool. The ethanolic HPC solution was then mixed with the aqueous solution of DTPA and the total weight adjusted to 100g with water.

Comparative Example C (see Table 1B) was prepared in a similar manner, with the omission of the DTPA and AMP.

Table 1B: PHMBS vs. PHMBS/DTPA (AMP salt)

Component		Example C	Example 1
PHMBS		0.043	0.043
DTPA		0	1.0
AMP		0	0.8
Ethanol		60	60
HPC		0.65	0.65
Water		to 100	to 100
Mean malodour intensity	5 hour	1.94	1.75
	24 hour	2.09	1.92

All components are expressed as weight per cent of the total components added. The malodour differences between the compositions were significant at the 99% level, after both 5 hours and 24 hours. (Minimum differences required for significance at the 95% and 99% confidence levels were: after 5 hours: 0.10 for 95% level; 0.13 for 99% level; after 24 hours: 0.09 for 95% level; 0.12 for 99% level). These results indicate that addition of DTPA/AMP salt to an anti-microbial composition also comprising PHMBS leads to an improved deodorancy performance.

It should also be noted that the above benefit for the composition of the invention was present even after 24 hours, indicating prolonged maintenance of malodour reduction, a direct result of the prolonged anti-microbial activity of the composition.

CLAIMS

1. An anti-microbial product comprising a transition metal chelator having an organic counter-ion and a further organic anti-microbial agent having a minimum inhibitory concentration (MIC) of 1 $mg.ml^{-1}$ or less.

2. An anti-microbial product according to claim 1, characterised in that the transition metal chelator and the further organic anti-microbial agent are both present in the same composition.

3. An anti-microbial product according to claim 1 or 2, that is also a deodorant product for use on the human body.

4. An anti-microbial product according to any preceding claim, characterised in that the further organic anti-microbial agent comprises a cationic anti-microbial agent.

5. An anti-microbial product according to any of the preceding claims, characterised in that the cation of the chelator salt is a protonated or quaternised amine with at least one N-substituent comprising a C_1-C_{10} terminal hydrocarbyl group.

6. An anti-microbial product according to claim 5, wherein the chelator salt is a salt of 2-amino-2-methyl-1-propanol, cyclohexylamine, diisopropanolamine, or 2-aminobutan-1-ol.

7. An anti-microbial product according to any of the preceding claims, wherein the transition metal chelator has affinity for iron (III).

8. An anti-microbial product according to claim 7, wherein the transition metal chelator has a binding coefficient for iron (III) of greater than 10^{26}.

9. An anti-microbial product according to any preceding claim, characterised in that the product is a single anti-microbial composition according to claim 2 and in that the liquid components of the composition comprise no greater than 50% by weight of water.

10. An anti-microbial product according to any preceding claim, characterised in that the transition metal chelator is a polyaminocarboxylic acid amine salt.

11. An anti-microbial product according to any preceding claim, characterised in that the transition metal chelator is a diethylenetriaminepentaacetic acid salt.

12. An anti-microbial product according to any of the above claims, characterised in that the further anti-microbial agent is bactericidal.

13. A method of controlling microbial numbers, said method comprising the application to a substrate of a transition metal chelator having an organic counter-ion and a further organic anti-microbial agent having a minimum inhibitory concentration (MIC) of 1 $mg.ml^{-1}$ or less.

14. A cosmetic method of inhibiting the generation of human body odour comprising the topical application to the skin of a product according any one of claims 1 to 12.

15. A method for the manufacture of an anti-microbial composition comprising the formation of a mixture of an organic anti-microbial agent having a minimum inhibitory concentration (MIC) of 1 $mg.ml^{-1}$ or less and the product of the at least partial neutralisation of an acidic transition metal chelator with an organic base.